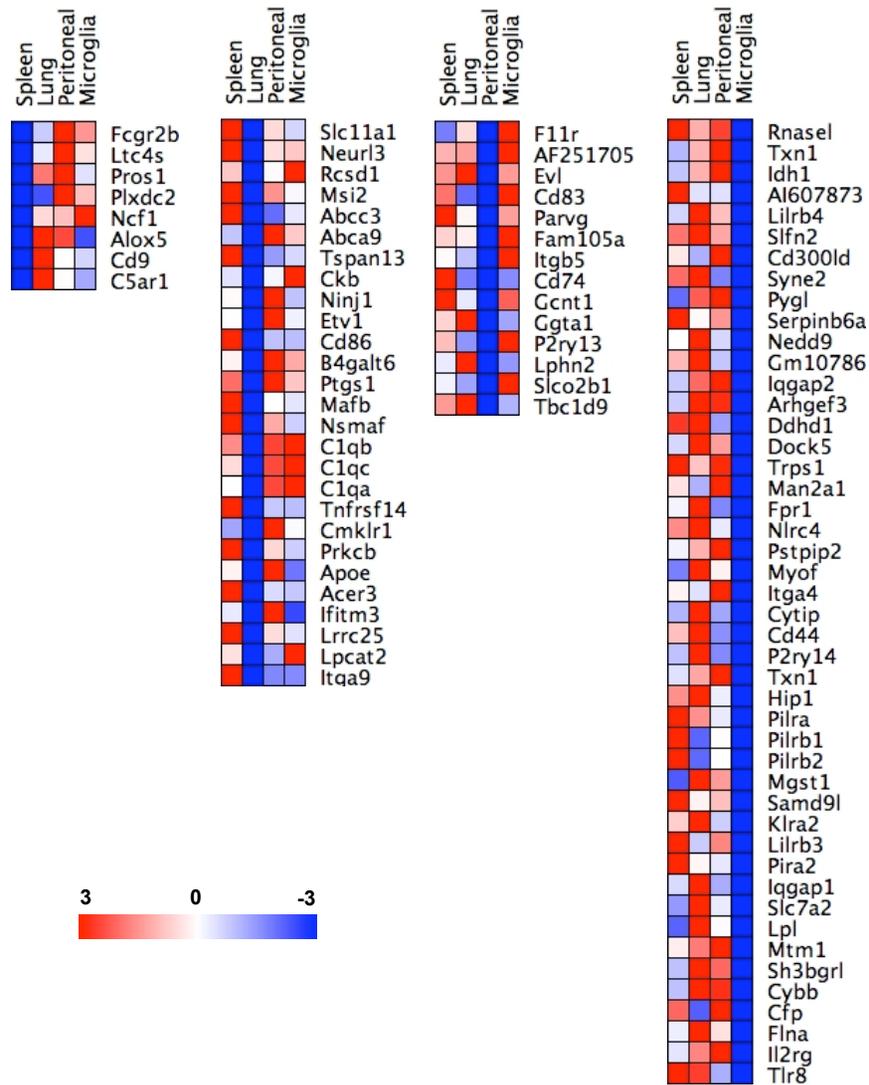
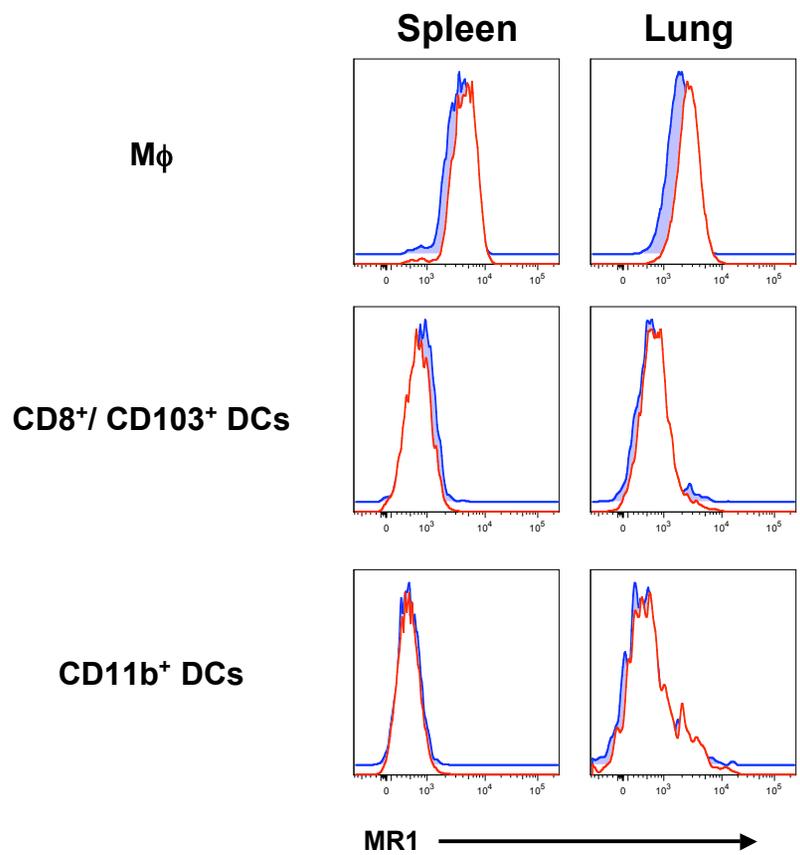


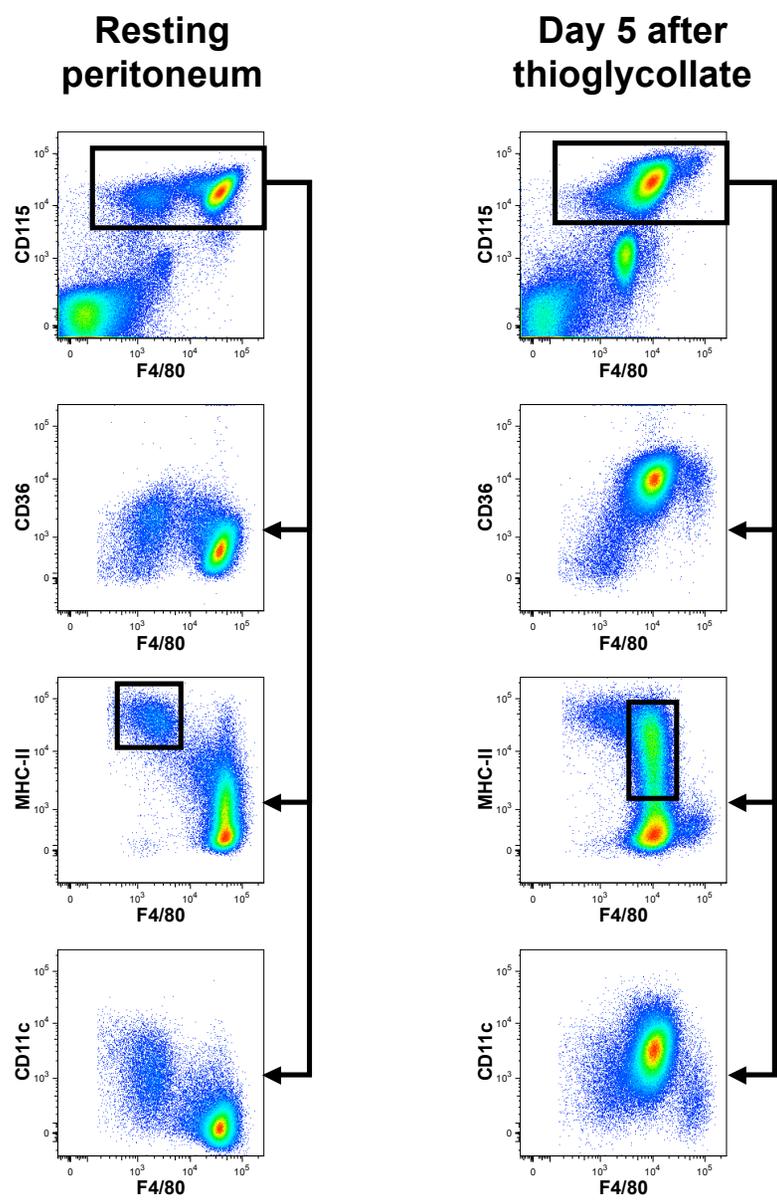
Supplementary Fig. 1



Supplementary Fig. 2



Supplementary Fig. 3



Supplementary Fig. 4

Supplementary Table 1. Pathway analysis of the specific gene expression profiles distinguishing different macrophages

Ingenuity Canonical Pathways	p-value	Molecules
Microglia		
HIF1 α Signaling	0.0005	SLC2A1, LDHB, MMP2, SLC2A5, EDN1, MMP14, VHL
Glioma Invasiveness Signaling	0.0078	PLAU, ITGB5, RHOH, MMP2
mTOR Signaling	0.0138	PPM1L, PRKAB1, RPTOR, RHOH, RPS6KA1, PRR5
Leukocyte Extravasation Signaling	0.0145	SIPA1, PLCG1, RHOH, MMP2, JAM3, MMP14, SELPLG
Communication between Innate and Adaptive Immune Cells	0.0148	CCL4, TNFRSF17, CCL3L1/CCL3L3, TLR9
Macropinocytosis Signaling	0.0148	PLCG1, ARF6, PDGFB, ITGB5
Crosstalk between Dendritic Cells and Natural Killer Cells	0.0214	PVRL2, FSCN1, TLR9, TREM2
Cysteine Metabolism	0.0282	LDHB, CHST11, CHST7
TREM1 Signaling	0.0331	CCL2, PLCG1, TLR9
Dendritic Cell Maturation	0.0398	HLA-DOB, FSCN1, HLA-DOA, TLR9, TREM2
Lung Macrophages		
Mitotic Roles of Polo-Like Kinase	0.0065	KIF23, CDC25B, KIF11, PPP2R1B, PRC1, CDC25A
Glycerolipid Metabolism	0.0078	LPIN1, LIPF, GLA, MGLL, GK, LPL, AKR1B1, DGAT2
Leukocyte Extravasation Signaling	0.0079	MMP19, ACTG1, CXCR4, SPN, MMP8, PRKCH, MMP12, BMX, CTNNA1, CLDN1, EZR, ITGAL
LPS/IL-1 Mediated Inhibition of RXR Function	0.0105	CPT1A, GSTM5, Gstm3, MGST3, ABCG1, IL1RL2, ALAS1, ACSL1, RARA, FABP1, HMGCS1, ACOX1
Fatty Acid Elongation in Mitochondria	0.0135	HSD17B4, EHHADH, Acaa1b
Cell Cycle Regulation by BTG Family Proteins	0.0182	PPP2R1B, CCNE1, CCNE2, CCRN4L
Cell Cycle: G1/S Checkpoint Regulation	0.0209	CDK6, CCNE1, CCNE2, CDC25A, RBL1
Sphingolipid Metabolism	0.0224	SGMS2, LPIN1, SPTLC2, GLA, NAAA, SULF2
Cyclins and Cell Cycle Regulation	0.0251	PPP2R1B, CDK6, CCNE1, CCNE2, CDC25A, CCNA2
Integrin Signaling	0.0275	ACTG1, NEDD9, ITGA5, ARHGAP26, CAPN2, ITGAX, GRB7, CAPN1, RHOF, BCAR3, ITGAL
p38 MAPK Signaling	0.0324	RPS6KA5, MAP3K5, IL1RL2, MAP4K1, MAPKAPK3, CREB5, IL1RN
Biosynthesis of Steroids	0.0380	FDFT1, SQLE, IDI1
Cell Cycle Control of Chromosomal Replication	0.0417	MCM4, CDK6, DBF4
FAK Signaling	0.0447	ACTG1, ITGA5, ARHGAP26, CAPN2, TNS1, CAPN1
Aryl Hydrocarbon Receptor Signaling	0.0457	GSTM5, Gstm3, MGST3, CDK6, CCNE1, CCNE2, RARA, CCNA2
cAMP-mediated signaling	0.0468	AKAP13, PTGER2, CXCR2, CAMK2G, CNR2, FPR2, CREB5, PRKAR2B, FPR1, P2RY14, AKAP5
Peritoneal Macrophages (F4/80^{hi})		
Eicosanoid Signaling	0.0005	PTGIR, DPEP2, PTGER4, ALOX15, PRDX6, PTGIS, PTGES
LXR/RXR Activation	0.0011	MSR1, APOE, ACACA, MMP9, APOC2, LBP, PLTP
IL-12 Signaling and Production in Macrophages	0.0012	TGFB2, IKBKE, CD40, ALOX15, AKT3, PRKD3, MST1R, STAT4
Acute Phase Response Signaling	0.0030	IKBKE, SAA1, FN1, CP, RRAS, AKT3, C4A/C4B, HP, LBP, CFB
N-Glycan Biosynthesis	0.0062	MAN1A1, FUT8, RPN2, ARSG, DAD1
TR/RXR Activation	0.0105	KLF9, ENO1, F10, ACACA, AKT3, HP
Virus Entry via Endocytic Pathways	0.0117	ITGA6, DNMT1, RRAS, FLNB, PRKD3, ITGB7
Glycolysis/Gluconeogenesis	0.0138	ALDH2, ENO1, ALDH1A2, HK1, PFKL, PDHA1
Riboflavin Metabolism	0.0191	ENPP5, ACPP, RFK
Human Embryonic Stem Cell Pluripotency	0.0200	TGFB2, FZD1, WNT2, S1PR1, AKT3, S1PR5, FGFR1
NF- κ B Activation by Viruses	0.0214	IKBKE, ITGA6, RRAS, AKT3, PRKD3
Aminosugars Metabolism	0.0251	PDE2A, CMAH, ALOX15, HK1, UAP1
PTEN Signaling	0.0251	TGFB2, IKBKE, RRAS, CCND1, AKT3, FGFR1
N-Glycan Degradation	0.0257	MAN1A1, GLB1, ENGASE
RAR Activation	0.0257	TGFB2, CYP26A1, ALDH1A2, RARB, ZBTB16, AKT3, PRKD3, RARG
Aryl Hydrocarbon Receptor Signaling	0.0269	TGFB2, NQO2, NFIA, ALDH1A2, RARB, CCND1, RARG
β -alanine Metabolism	0.0275	ALDH2, ALDH1A2, DPYSL3, HIBCH
Wnt/ β -catenin Signaling	0.0282	TGFB2, TGFB2, FZD1, RARB, WNT2, CCND1, AKT3, RARG
Histidine Metabolism	0.0295	ALDH2, HAL, ALDH1A2, HDC
Glycosphingolipid Biosynthesis	0.0302	ST3GAL4, GLB1, ST3GAL5
Complement System	0.0302	CFH, C4A/C4B, CFB
Inhibition of Angiogenesis by TSP1	0.0355	THBS1, MMP9, AKT3
P2Y Purigenic Receptor Signaling Pathway	0.0380	P2RY1, PLCB4, RRAS, AKT3, PRKD3, GNG12
Coagulation System	0.0380	F10, F5, F13A1
Butanoate Metabolism	0.0407	ALDH2, ALDH1A2, PRDX6, PDHA1
G-Protein Coupled Receptor Signaling	0.0417	PDE2A, RGS18, PTGER4, P2RY1, RRAS, S1PR1, AKT3, CMKLR1, PTGIR, IKBKE, FZD1, EDNRB, GPRC5B, CXCR7, PLCB4, HTR2A, S1PR5
Glycosaminoglycan Degradation	0.0479	HPSE, GLB1, ALOX15
Spleen Red Pulp Macrophages		
Interferon Signaling	0.0004	IRF1, STAT1, MX1, STAT2, IFIT3
Communication between Innate and Adaptive Immune Cells	0.0006	Tlr11, CD86, IL15, HLA-DRB1, TLR1, CD4, IL1B
Dendritic Cell Maturation	0.0007	HLA-DQB1, CD86, IL15, STAT1, HLA-DRB1, MAPK8, STAT2, HLA-DQA1, CD1D, IL1B
Primary Immunodeficiency Signaling	0.0013	CIITA, CD4, ICOS, DCLRE1C, ADA
Graft-versus-Host Disease Signaling	0.0014	HLA-DQB1, CD86, HLA-DRB1, HLA-DQA1, IL1B
IL-15 Production	0.0020	IRF1, IL15, STAT1, PTK2
LPS/IL-1 Mediated Inhibition of RXR Function	0.0029	ABCC3, GSTA4, HS3ST2, CHST15, IL1R1, MAPK8, UST, ACSL3, NDST1, NR1H3, IL1B
Chondroitin Sulfate Biosynthesis	0.0030	HS3ST2, CHST15, UST, NDST1, DSE
Antigen Presentation Pathway	0.0032	CIITA, HLA-DRB1, CD74, HLA-DQA1
Cysteine Metabolism	0.0034	GOT1, HS3ST2, CHST15, UST, NDST1
Keratan Sulfate Biosynthesis	0.0037	HS3ST2, CHST15, WDFY3, UST, NDST1
Activation of IRF by Cytosolic Pattern Recognition Receptors	0.0048	IFIH1, STAT1, MAPK8, STAT2, IRF7
Glycerolipid Metabolism	0.0051	AOAH, Akr1b7, DGKI, ADHFE1, MOGAT1, PPAP2B, PPAP2A
Role of JAK2 in Hormone-like Cytokine Signaling	0.0058	SOC55, STAT1, EPOR, HLTf
Role of Pattern Recognition Receptors in Recognition of Bacteria and Viruses	0.0063	Tlr11, IFIH1, NOD1, TLR1, IRF7, IL1B
Phospholipid Degradation	0.0107	GDPD1, DGKI, PLCL1, HMOX1, PPAP2B, PPAP2A
Cdc42 Signaling	0.0195	HLA-DQB1, EXOC6, HLA-DRB1, MAPK8, VAV2, HLA-DQA1, H2-T24
Xenobiotic Metabolism Signaling	0.0200	ABCC3, GSTA4, HS3ST2, CHST15, MAPK8, UST, AHR, HMOX1, NDST1, MAF, IL1B
Glycerophospholipid Metabolism	0.0209	GDPD1, GOT1, DGKI, PLCL1, HMOX1, PPAP2B, PPAP2A
Sphingolipid Metabolism	0.0229	ARSI, UGCG, GALC, PPAP2B, PPAP2A
TREM1 Signaling	0.0229	Tlr11, CD86, TLR1, IL1B
Complement System	0.0302	CD55, C6, C2
FXR/RXR Activation	0.0372	CYP27A1, MAPK8, ABCB4, NR1H3, IL1B
Fcy Receptor-mediated Phagocytosis in Macrophages and Monocytes	0.0457	FYB, FYN, VAV2, HMOX1, PTEN
Leukocyte Extravasation Signaling	0.0457	DLC1, VCAM1, PECAM1, MAPK8, MMP13, VAV2, MMP27, PTK2

Supplementary Table 2. Analysis of modules significantly enriched in macrophage-associated genes

	Macrophage populations	Fine module	hypergeometric p-value	overlap size	overlap genes
All 4 macrophage population	all	112	3.21E-05	4	CD14;CTSL;SEPP1;TMEM195
		125	1.80E-04	3	COMT1;PLOD1;TCN2
		130	1.12E-06	4	TLR4;TMEM77;TOM1;TPP1
		161	4.18E-12	6	A930039A15RIK;CAMK1;GLUL;MYO7A;PLA2G15;PON3
	w/o Peritoneum	165	4.26E-05	3	GPR77;IL1A;TMEM86A
	w/o Lung	168	1.26E-05	3	C1QA;C1QB;C1QC
	w/o Microglia	132	5.29E-11	7	C130050O18RIK;FCGR4;HGF;PILRA;PILRB1;PILRB2;TLF
		165	1.98E-04	3	LPL;MITF;SNX24
w/o Spleen	122	8.73E-08	4	CEBPB;DHRS3;PLOD3;PROS1	
Two macrophage populations	Peritoneum and Spleen	165	1.02E-05	4	2810405K02RIK;GM4951;GM5970;IGF1
		295	7.60E-05	3	ASPA;CD5L;FCNA
	Peritoneum and Lung	122	3.59E-05	4	CEBPB;DRAM1;DUSP3;FN1
		164	4.63E-06	4	CLEC4E;F10;GDA;PLCB1
		166	6.05E-10	6	ALOX5;ATG7;G6PDX;PGD;PRDX5;SEPX1
		188	2.02E-04	3	CAV1;FZD4;PDK4
	Lung and Spleen	133	3.37E-07	5	CLEC4A3;EAR1;EAR10;GM5150;SIGLEC1
	Peritoneum and Microglia	x	x	x	x
Lung and Microglia	168	4.19E-07	4	HPGDS;P2RY12;SLC40A1;SLC7A8	
Microglia and Spleen	128	5.14E-06	3	ANG;SERPINE1;X99384	

Supplementary Table 3. Function and other information on the 11 genes that comprise module 161.

Gene/Name	Function/Other Informations
Akr1b10, aldo-keto reductase family1 member B10	ubiquitin-dependent degradation of acetyl-coA carboxylase a; key role in regulating phospholipids composition in cells, reactive oxygen species, and cell survival.
Blvrb, biliverdin IX beta reductase	Converts biliverdin to bilirubin
Camk1; calcium/calmodulin-dependent kinase 1	Major signaling intermediate
Glul; glutamate-cysteine ligase (also called GCL)	Catalyzes the rate-limiting step in glutathione synthesis.
Myo7a (myosin VIIA)	Intracellular trafficking of vesicles to the lysosome (mutations cause Usher's syndrome)
Nln, neurolysin. Also called oligopeptidase M.	metallo carboxypeptidase in the same family as angiotensin-converting enzyme
Pcyox1, prenyl cysteine oxidase 1.	Catabolism of prenylcysteines
Pla2g15, group XV phospholipase A2	lysosomal phospholipase A2; regulates phospholipid content/distribution.
Pon3, paroxonase 3.	Paroxonases have lactonase activity and serve as anti-oxidants. PON3 is mainly found on HDL.
Slc48a1, solute carrier family 48 (heme transporter), member 1	Heme transporter that regulates intracellular heme availability/degradation through the endosomal or lysosomal compartment.
A930039A15Rik	unknown

Supplementary Table 4. Fine modules and predicted regulators of specific macrophage populations in different organs.

	Tissue macrophage population			
	Spleen Red Pulp	Lung	Peritoneal	Microglia
Fine module #	330	296	295, 111, 112	194, 314
Predicted regulators	SpiC	PPAR γ	Gata6	MafB, ZFHX3, ZFP715, Bhlhe41